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Lynch Syndrome-associated Genomic Variants

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ABSTRACT

Background & Aims: Lynch Syndrome, a hereditary disorder characterized by germline mutations in mismatch repair (MMR) genes, is a major contributor to colorectal cancers. It has also been identified in endometrial cancer. Despite the established role of MMR deficiency in tumorigenesis, the specific genomic alterations driving Lynch syndrome-associated endometrial cancer, and their overlap with colorectal cancer, remain incompletely understood. This study aims to fill this gap by performing a detailed comparative analysis of germline and somatic mutations in endometrial cancer within the context of Lynch syndrome.

Methods: We conducted whole exome sequencing on matched germline and somatic DNA from 13 patients diagnosed with Lynch syndrome-associated endometrial cancer. High-depth sequencing was performed, followed by rigorous bioinformatics analysis to identify and annotate variants, focusing on their potential pathogenicity and relevance to both endometrial and colorectal cancer.

Results: Our analysis revealed 1,118 germline and 14,051 somatic variants, with 493 variants common to both. Recurrent pathogenic mutations in *MLH1, MSH2*, and *MSH6* were confirmed, highlighting their critical role in Lynch syndrome. Notably, frequent somatic mutations in the *PIK3CA* and *PTEN* genes were identified, implicating the PI3K/AKT/mTOR pathway as a key oncogenic driver in these cancers. Additionally, novel somatic mutations in genes related to the extracellular matrix such as *FBN1* and *SPARC* were uncovered, suggesting a possible unique role in endometrial tumor progression.

Conclusions: This study provides new insights into the molecular basis of Lynch syndrome-associated endometrial cancer, emphasizing the overlap in oncogenic pathways with colorectal cancer. The discovery of shared and unique genetic mutations highlights the importance of developing combined treatment strategies and suggests that targeting these specific mutations could improve therapy for patients with Lynch syndrome-associated cancers.

Key words: Lynch syndrome – whole exome sequencing – mismatch repair genes – somatic variants – germline variants – personalized medicine – colorectal cancer.

Abbreviations: ACMG: American College of Medical Genetics; ARID1A: AT-rich interaction domain 1A; ASS1: argininosuccinate synthase 1; BAM: binary alignment map; BER: base excision repair; DNA: deoxyribonucleic acid; ECM: extracellular matrix; EDTA: ethylenediaminetetraacetic acid; EDAR: ectodysplasin A receptor; EXO1: exonuclease 1; FASTA: Fast-All; FASTQ: FASTA with quality; FBN1: fibrillin 1; FFPE: formalin-fixed paraffin-embedded; FIGO: International Federation of Gynecology and Obstetrics; GDPR: General Data Protection Regulation; HGVSc: Human Genome Variation Society nomenclature; HNPCC: hereditary nonpolyposis colorectal cancer; KCTD7: potassium channel tetramerization domain containing 7; KRAS: Kirsten rat sarcoma virus; MLH1: mutL homolog 1; MMR: mismatch repair; MSH2: mutS homolog 2; MSH6: mutS homolog 6; MSI: microsatellite instability; MUTYH: mutY DNA glycosylase; NAGLU: alpha-N-acetylglucosaminidase; NGS: next generation sequencing; PD-1: programmed cell death protein 1; PI3K: phosphoinositide 3-kinase; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; POLE: polymerase epsilon; POLD1: polymerase delta 1; PMS2: postmeiotic segregation increased 2; PTEN: phosphatase and tensin homolog; SERPINC1: serpin family C member 1; SETD2: SET domain containing 2; SMARCA4: SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4; SNP: single nucleotide polymorphism; SPARC: secreted protein acidic and rich in cysteine; VCF: variant call format; WES: whole exome sequencing.

INTRODUCTION

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant disorder that significantly increases the risk of developing various cancers, including colorectal, endometrial, ovarian, gastric, and others [1]. The hereditary nature of Lynch syndrome is primarily due to germline mutations in the DNA mismatch repair (MMR) genes, which are integral to maintaining genomic stability by correcting DNA replication errors [2].

The MMR system is a highly conserved pathway across species, crucial for the recognition and repair of base-base mismatches and insertion-deletion loops that occur during DNA replication. The core MMR genes implicated in Lynch syndrome include mutL homolog 1 (*MLH1*), mutS homolog 2 (*MSH2*), mutS homolog 6 (*MSH6*), and postmeiotic segregation increased 2 (*PMS2*), with mutations in *MLH1* and *MSH2* accounting for the majority of cases [3]. These genes encode proteins that form heterodimers essential for the MMR function: *MLH1* pairs with *PMS2*, while *MSH2* pairs with *MSH6* or *MSH3* [3]. The loss of function in any of these proteins due to germline mutations leads to a defective MMR system, resulting in microsatellite instability (MSI) and an increased mutation rate throughout the genome [4].

Microsatellite instability (MSI), a hallmark of Lynch syndrome-associated cancers, is characterized by the accumulation of mutations in short, repetitive DNA sequences known as microsatellites [5]. This instability is a direct consequence of the impaired MMR system and serves as a critical biomarker for the diagnosis of Lynch syndrome [6, 7]. The presence of MSI in tumors, particularly in colorectal and endometrial cancers, is a strong indicator of underlying MMR deficiency and, by extension, Lynch syndrome [8]. The identification of MSI has significant clinical implications, including guiding the use of immunotherapy, which has shown promise in treating MSI-high cancers due to their high mutational burden and resultant neoantigen production [9, 10].

However, the mere presence of a germline MMR mutation does not guarantee cancer development [11]; it is the accumulation of additional somatic mutations that dictates whether and when cancer will emerge [12]. This „second-hit" hypothesis underscores the importance of somatic mutations in the carcinogenic process, particularly in tissues already predisposed by a germline mutation [13].

The somatic landscape of Lynch syndrome-associated cancers, particularly endometrial cancer, remains incompletely characterized. While MSI is a hallmark of these tumors [5, 8], driven by the failure of MMR [2, 4], the specific somatic mutations that accompany or follow the onset of MSI are not fully understood. These mutations may involve critical oncogenes and tumor suppressor genes that further destabilize the genome, promoting malignant transformation and progression [14]. For example, mutations in genes such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), phosphatase and tensin homolog (*PTEN*), and Kirsten rat sarcoma virus (*KRAS*) have been observed in endometrial cancer [15], but their prevalence and impact within the context of Lynch syndrome are not yet fully elucidated. Understanding these somatic changes is vital not only for comprehending the full scope of molecular alterations in Lynch syndrome-associated cancers but also for identifying potential targets for therapeutic intervention.

Moreover, the identification of germline mutations has significant implications for cancer screening and prevention strategies, particularly in familial settings. Patients with Lynch syndrome benefit from regular surveillance for various cancers, which is often detected at an earlier stage due to proactive screening [16-18]. However, the discovery of somatic mutations can further refine these strategies, potentially leading to more personalized surveillance protocols based on the specific mutational profile of the tumor. The dual analysis of germline and somatic mutations also plays a crucial role in the realm of treatment. Tumors with high MSI due to MMR deficiency, as commonly seen in Lynch syndrome, have been shown to respond well to immune checkpoint inhibitors, such as anti-programmed cell death-1 (PD-1) therapies [19].

Exploring the genomic landscape of Lynch syndrome-associated endometrial cancer is essential to understanding the molecular mechanisms driving tumorigenesis in these patients, distinct from sporadic cases. This knowledge can guide personalized treatments and improve surveillance strategies. Despite the known link between Lynch syndrome and endometrial cancer, a comprehensive analysis of somatic and germline mutations specific to this context is lacking.

This study addresses this gap by using whole exome sequencing (WES) to analyze both germline and somatic mutations in patients with Lynch syndrome-associated endometrial cancer. By comparing normal and tumor tissues, we aim to identify key mutations driving cancer in this high-risk group. The findings could reveal novel biomarkers and therapeutic targets, advancing precision medicine in treating Lynch syndrome-associated endometrial cancer.

METHODS

We approached Lynch syndrome from the side of cases with endometrial cancer. The study cohort consisted of 13 female patients diagnosed with endometrial cancer, with ages ranging from 47 to 75 years and a mean age of 60 years at the time of diagnosis. All patients had a confirmed histopathological diagnosis of endometrial cancer, and tumor staging was conducted in accordance with the International Federation of Gynecology and Obstetrics (FIGO) system. The tumors were uniformly classified as endometrioid adenocarcinoma, the most prevalent histological subtype associated with Lynch syndrome in endometrial cancer. The inclusion and exclusion criteria are shown in Table I.

Table I. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Histopathologically confirmed endometrial cancer	Insufficient/degraded DNA
Availability of germline and tumor samples	Presence of other active malignancies
Provided informed consent	Inadequate clinical data

Whole exome sequencing analysis was performed on DNA derived from blood and FFPE tissue samples of the included patients. The sequencing was performed by CeGaT GmbH (Tübingen, Germany), following their standard protocols. Peripheral blood samples (5 mL) from each patient were collected in EDTA tubes, and DNA was extracted using the QIAGEN Symphony DSP DNA Mini Kit 96, yielding concentrations between 30.193 and 70.365 ng/μL. FFPE tumor samples, collected as per CeGaT's guidelines, were processed with the MagMax FFPE DNA/RNA Ultra Kit, resulting in DNA concentrations ranging from 45.700 to 134.000 ng/μL. All samples met quality control criteria and were used for library preparation with the CeGaT Exome V5 kit. Sequencing on the Illumina NovaSeq 6000 platform achieved an average exome coverage depth of 100x, with over 95% of targeted bases covered at a depth of at least 20x, ensuring high-quality data with Q30 values exceeding 89.78%.

Bioinformatics analysis was conducted using the Geneyx Analysis platform (Geneyx Genomex Ltd., Israel), version 6, where FASTQ files were aligned to the GRCh38 human reference genome using the DRAGEN (Dynamic Read Analysis for GENomics) pipeline (Illumina, Inc., USA), version 3.7.5. Variants were called, annotated, and filtered for relevance to Lynch syndrome and endometrial cancer. High-priority variants were interpreted according to the American College of Medical Genetics (ACMG) guidelines, with Fisher's Exact Test and odds ratio calculations applied to assess their significance. The results, integrated with clinical data, provided insights into the genetic basis of Lynch syndrome-associated endometrial cancer, highlighting potential targets for personalized therapy. Data, including binary alignment map (BAM) and variant call format (VCF) files, were securely stored on cloud-based platforms in compliance with GDPR guidelines.

Ethical Approval

The study was approved by the Ethics Committee of the Alessandrescu-Rusescu National Institute of Mother and Child Health, Bucharest, Romania (approval number/ 14969/23.09.2019). The study adhered to the principles of the Declaration of Helsinki of the World Medical Association on human studies, 2013.

RESULTS

Through WES of matched germline blood samples and FFPE tumor samples, we identified a diverse range of genomic variants contributing to the pathogenesis of endometrial cancer. A total of 1,118 germline variants and 14,051 somatic variants were identified across the cohort. Of these, 493 variants were common to both germline and tumor samples, suggesting potential roles in both inherited predisposition and somatic tumorigenesis. Additionally, 625 variants were unique to the germline, while 13,558 variants were uniquely somatic, highlighting the distinct genomic alterations associated with cancer progression.

Table II provides a detailed annotation of the top common while Table 3 highlights key unique germline and somatic variants identified in our study. The variants included in the tables were selected based on their clinical relevance, potential for targeted therapy, recurrence within the cohort, and strong support from existing literature.

Table II. Annotation of clinically relevant top common variants in Lynch syndrome-associated endometrial cancer

Gene	Variant (HGVSc)	Variant type	Pathogenicity classification	Known function	Clinical significance	Relevant literature
MLH1	(p.Gly226Asp)	Missense	Pathogenic	Mismatch repair	Disrupts MLH1-PMS2 interaction, leading to MMR deficiency	Lynch HT et al. [20]
MSH2	c.942+3A>T	Splice site	Pathogenic	Mismatch repair	Aberrant splicing, resulting in a truncated, non-functional protein	Morak M et al. [21]
MSH6	c.3261dupC	Frameshift	Pathogenic	Mismatch repair	Results in truncated protein, loss of MMR function	Kantelinen J et al. [22]
PIK3CA	c.3140A>G (p.His1047Arg)	Missense	Pathogenic	PI3K/AKT/ mTOR	Constitutive activation of PI3K signaling, driving oncogenesis	Yuan TL et al. [23]
PTEN	c.389G>A (p.Arg130Gln)	Missense	Pathogenic	Tumor suppression	Loss of phosphatase activity, promoting cell proliferation	Mondal SK et al. [24]
FBN1	c.8326C>T	Missense	Pathogenic	ECM structure	Alters ECM dynamics, potentially enhancing tumor invasion	Mahdizadehi M et al. [25]
POLE	c.1373A>G (p.Tyr458Cys)	Missense	Likely pathogenic	DNA replication	Associated with hypermutated phenotype, better immunotherapy response	McConechy MK et al. [26]
POLD1	c.1433G>A (p.Arg477His)	Missense	Likely pathogenic	DNA replication	May contribute to increased replication errors, leading to genomic instability	Church DN et al. [27]
SERPINC1	c.236G>A (p. Arg79His)	Missense	Likely pathogenic	Coagulation	Potentially linked to hypercoagulability and tumor growth	Alhenc-Gelas M et al. [28]
SPARC	c.1024_1025del	Frameshift	Likely pathogenic	ECM regulation	May enhance tumor invasion and angiogenesis	Chlenski A et al. [29]

ASS1: argininosuccinate synthase 1; ECM: extracellular matrix; FBN1: fibrillin 1; HGVSc: the variant description according to Human Genome Variation Society nomenclature; MLH1: mutL homolog 1; MMR: mismatch repair; MSH2: mutS homolog 2; MSH6: mutS homolog 6; PI3K: phosphoinositide 3-kinase; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; POLE: polymerase epsilon; POLD1: polymerase delta 1; PMS2: postmeiotic segregation increased 2; PTEN: phosphatase and tensin homolog; SERPINC1: serpin family C member 1; SPARC: secreted protein acidic and rich in cysteine.

Table III. Key unique germline and somatic variants with potential clinical relevance

Source	Gene	Variant (HGVSc)	Variant type	Pathogenicity classification
Germline	*MLH1*	c.1852_1854del (p.Lys618del)	In-frame deletion	Pathogenic
Germline	*MSH2*	c.1030C>T (p.Arg344*)	Nonsense	Pathogenic
Germline	*POLE*	c.1373A>G (p.Tyr458Cys)	Missense	Likely pathogenic
Germline	*POLD1*	c.1433G>A (p.Arg477His)	Missense	Likely pathogenic
Somatic	*PIK3CA*	c.3140A>G (p.His1047Arg)	Missense	Pathogenic
Somatic	*PTEN*	c.389G>A (p.Arg130Gln)	Missense	Pathogenic
Somatic	*FBN1*	c.8326C>T	Missense	Pathogenic
Somatic	*SPARC*	c.1024_1025del	Frameshift	Likely pathogenic
Somatic	*SERPINC1*	c.236G>A (p.Arg79His)	Missense	Likely pathogenic
Somatic	*ASS1*	c.911G>A (p.Gly304Asp)	Missense	Likely pathogenic

For abbreviations see Table II.

Common Variants

Among the 493 common variants identified across both germline and somatic exomes in our cohort, a significant portion were associated with genes implicated in Lynch syndrome and related DNA repair pathways. One patient exhibited a pathogenic *MLH1* c.677G>A (p.Gly226Asp) variant, detected both in the germline and somatic samples. This variant is well-documented in Lynch syndrome and is known to severely disrupt the MMR function by impairing the interaction of *MLH1* with its binding partners. Similarly, variants in *MSH2* and *MSH6* were identified in multiple patients. A particularly noteworthy *MSH2* variant, c.942+3A>T, was found in three patients. This splice site mutation likely leads to aberrant splicing, resulting in a truncated or dysfunctional protein, further compromising MMR activity. In the somatic context, these patients exhibited additional mutations in other MMR-related genes, such as *MLH3* and exonuclease 1 (*EXO1*), suggesting a progressive accumulation of DNA repair deficiencies contributing to genomic instability and cancer progression.

Beyond the well-established Lynch syndrome genes, our analysis also uncovered common variants in genes not traditionally associated with Lynch syndrome but involved in related pathways that might influence cancer risk and progression. For instance, variants in polymerase delta 1 (*POLD1*) and polymerase epsilon (*POLE*), which encode key subunits of DNA polymerase involved in replication and repair, were identified in several patients. A recurrent *POLE* variant, c.1373A>G (p.Tyr458Cys), was found in both germline and tumor samples of two patients. We also identified a variant in BRAF (c.1799T>A, p.Val600Glu) in both the germline and tumor samples of one patient. While *BRAF* mutations are more commonly associated with sporadic microsatellite instability-high (MSI-H) cancers, their presence in a Lynch syndrome patient suggests a possible interplay between inherited MMR deficiencies and somatic activation of oncogenic pathways.

Germline and Somatic Variants

The germline analysis of the patients identified 1,118 variants, including SNPs and indels, across several key genes. Pathogenic or likely pathogenic variants in *MLH1* and *MSH2* were found in 5 patients, confirming their role in cancer predisposition. Additionally, variants in other DNA repair genes like *EXO1*, *POLD1*, and *POLE* were detected, though their contribution to Lynch syndrome requires further investigation. Interestingly, mutations in genes less traditionally linked to Lynch syndrome, such as *MUTYH*, *ARID1A*, and *SMARCA4*, suggest potential novel genetic contributors to endometrial cancer risk. The tumor exome analysis revealed 14,051 somatic variants, reflecting significant genomic instability. Frequently observed mutations in *PIK3CA* and *PTEN*, affecting the PI3K/AKT/mTOR pathway, were present in over 70% of tumors. Additionally, somatic mutations in chromatin remodeling genes *ARID1A* and *SMARCA4*, as well as MMR-associated genes like *SETD2* and *RNF43*, further implicate defective DNA repair and chromatin structure alterations in tumorigenesis. The comparison between germline and somatic exomes revealed 493 common variants, including a pathogenic *MLH1* variant, indicating a clonal relationship between inherited predispositions and somatic tumor progression.

Unique Germline Variants

The analysis of the germline exomes from our cohort revealed a total of 625 unique variants. These variants represent the inherited genetic background that may predispose individuals to cancer development, particularly in the context of Lynch syndrome. A significant focus was placed on identifying and characterizing variants in MMR genes. The most frequently mutated genes in this category were *MLH1*, *MSH2*, and *MSH6*, with variants detected in 8 out of the 13 patients. The most notable variant in *MLH1* was the c.1852_1854del (p.Lys618del) mutation, observed in 3 patients. In *MSH2*, the c.942+3A>T splice site mutation was found in 4 patients, leading to abnormal splicing and likely resulting in a truncated protein that lacks functional MMR activity. Additionally, we identified the c.1030C>T (p.Arg344*) nonsense mutation in *MSH2* in one patient, which introduces a premature stop codon and is predicted to result in a non-functional protein. Variants in *MSH6* included the c.3261dupC (p.Ile1088Hisfs*4) frameshift mutation, found in 2 patients. This frameshift leads to a truncated protein that is incapable of participating in the MMR process, consistent with the pathogenic role of *MSH6* in Lynch syndrome. The presence of this variant in the germline of these patients underscores its importance in hereditary cancer predisposition.

Beyond the core MMR genes, the analysis also revealed pathogenic or likely pathogenic variants in other genes with roles in DNA repair, chromatin remodeling, and signal transduction, which could contribute to cancer susceptibility in this cohort. We identified a c.1433G>A (p.Arg477His) variant in *POLD1* in one patient and a c.1373A>G (p.Tyr458Cys) variant in *POLE* in another. Both of these variants are located in the exonuclease domain of their respective DNA polymerases, crucial for proofreading and maintaining replication fidelity. The presence of these mutations suggests a possible increase in replication errors, leading to a hypermutated phenotype observed in the tumors of these patients. Variants in chromatin remodeling genes *ARID1A* and *SMARCA4* were also detected. The c.4390C>T (p.Gln1464*) nonsense mutation in *ARID1A* was found in one patient and is predicted to result in a loss-of-function protein. The base excision repair (BER) pathway gene *MUTYH* harbored the c.1187G>A (p.Gly396Asp) variant in 2 patients. This variant is known to compromise the repair of oxidative DNA damage, which could lead to an accumulation of mutations and contribute to cancer development.

Unique Somatic Variants

The tumor exome analysis of the patients revealed a complex landscape of 13,558 unique somatic variants included in a wide range of functional categories, including single nucleotide polymorphisms (SNPs), small insertions/deletions (indels), and larger structural variants. A significant portion of these mutations were found in genes associated with cancer-related pathways. *PIK3CA* mutations were among the most frequently observed somatic alterations, detected in 9 out of 13 tumors. The most common mutation was c.3140A>G (p.His1047Arg), a well-characterized hotspot mutation that leads to constitutive activation of the PI3K/AKT/mTOR pathway, driving cell proliferation and survival. Similarly, *PTEN* mutations were identified in 7 tumors, with the c.389G>A (p.Arg130Gln) variant being the most recurrent. This mutation disrupts the phosphatase activity of *PTEN*, further enhancing PI3K/AKT signaling and contributing to tumorigenesis. A pathogenic somatic variant in FBN1 was identified in 3 tumors. The *ASS1* gene harbored a likely pathogenic c.911G>A (p.Gly304Asp) variant in 2 tumors. A likely pathogenic variant in *EDAR* (c.265C>T, p.Thr89Met) was identified in one tumor. *EDAR* is a member of the TNF receptor family, and while its role in cancer is not fully understood, it may be involved in modulating apoptosis or immune responses in the tumor microenvironment. The *KCTD7* gene was found to have a c.550C>T (p.Arg184Trp) variant in one tumor. The *NAGLU* gene, encoding alpha-N-acetylglucosaminidase, showed a c.419A>G (p.Tyr140Cys) variant in two tumors. *NAGLU* plays a role in lysosomal degradation, and its disruption may contribute to the accumulation of glycosaminoglycans, affecting cell signaling and tumor progression. Another likely pathogenic variant in *SERPINC1* (c.236G>A, p.Arg79His) was identified in one tumor. The *SPARC* gene, involved in the extracellular matrix (ECM) interaction, harbored a c.1024_1025del variant in two tumors.

By comparing the somatic variants with the germline data, we identified 13,558 somatic mutations exclusive to the tumor samples. These somatic-exclusive variants provide critical insights into the tumorigenic processes that occur independently of inherited predispositions. Notably, several somatic mutations in genes such as *PIK3CA*, *PTEN*, and *FBN1* were not present in the germline, highlighting their role in the acquired genomic alterations that drive endometrial cancer progression.

DISCUSSION

Lynch syndrome is responsible for a part of colorectal and other cancers. Its identification is important to prevent the onset or progress of these cancers. The presence of pathogenic variants in key MMR genes such as *MLH1*, *MSH2*, and MSH6 in both germline and somatic samples that we studied, underscores their essential role in Lynch syndrome. These variants are well-documented drivers of MMR deficiency, leading to microsatellite instability (MSI) and an increased mutation burden [5, 8, 30].

The common variants identified in our cohort, particularly in *MLH1* (e.g., c.677G>A, p.Gly226Asp), suggest a clonal relationship between the inherited MMR deficiency and subsequent somatic mutations that drive tumor progression. This finding aligns with previous studies that have demonstrated the critical role of MMR gene mutations in the early stages of Lynch syndrome-associated tumorigenesis [6, 31, 32].

Recurrent detection of pathogenic variants such as *MLH1* c.1852_1854del (p.Lys618del) and *MSH2* c.942+3A>T highlights the heterogeneity of Lynch syndrome mutations and their probable contribution to cancer risk [33-35], consistent with previous research that have established these mutations as high-risk factors for Lynch syndrome-associated cancers, further validating their critical role in the disease process. This underscores the importance of incorporating these genetic markers into routine diagnostic screening, as early identification of pathogenic germline variants could facilitate timely surveillance and intervention, potentially improving outcomes. Additionally, the inclusion of next-generation sequencing (NGS) panels that cover a broader range of DNA repair and chromatin remodeling genes could enhance the detection of at-risk individuals who might otherwise be missed by traditional screening methods [36-38].

The identification of unique germline variants in other DNA repair and chromatin remodeling genes, such as *POLD1*, *POLE* [39] and *ARID1A* [40], suggests additional layers of genomic instability in Lynch syndrome patients. Given *ARID1A*'s role in chromatin remodeling and tumor suppression [41, 42], its inactivation may contribute to the dysregulation of gene expression and increased oncogenic potential in endometrial cells. We hypothesize that the presence of these variants may contribute to a heightened risk of cancer development by further compromising genomic integrity, even in the absence of overt MMR deficiency. This finding aligns with emerging research suggesting that Lynch syndrome may involve a broader spectrum of genetic alterations beyond the MMR genes [34, 43]. Previous studies have shown that tumors with a hypermutated phenotype, often associated with *POLE* and *POLD1* mutations, tend to have higher levels of neoantigens and are more likely to respond to PD-1/PD-L1 blockade [44-46]. Expanding genetic testing panels to include genes like

POLD1, *POLE*, and other DNA repair genes could improve the accuracy of risk assessment and help identify individuals at risk of developing more aggressive or treatment-resistant forms of endometrial cancer.

Our discovery of 14,051 unique somatic variants provides a detailed view of the somatic alterations driving tumorigenesis in Lynch syndrome-associated endometrial cancer. While Lynch syndrome-associated colorectal and endometrial cancers share a common genetic foundation, our study also highlights distinct differences in the somatic mutations that characterize each cancer type. For instance, mutations in *APC* and *KRAS*, which are frequently observed in colorectal cancer [47, 48], were not prominent in our endometrial cancer cohort.

We found a high prevalence of *PIK3CA* c.3140A>G (p.His1047Arg) and *PTEN* c.389G>A (p.Arg130Gln) mutations that aligns with the established role of the PI3K/AKT/mTOR pathway in endometrial cancer [49]. These mutations, which contribute to uncontrolled cell proliferation and survival, highlight their importance as therapeutic targets [50, 51]. Interestingly, the identification of somatic mutations in genes traditionally associated with hereditary connective tissue disorders, such as FBN1 c.8326C>T, suggests that alterations in ECM-related genes may influence the tumor microenvironment, potentially contributing to cancer cell invasion and metastasis [52, 53]. This points to potential differences in the tumor microenvironment between endometrial and colorectal cancer. ECM remodeling has not been extensively studied in the context of Lynch syndrome-associated colorectal cancer, where the tumor microenvironment is influenced more by factors such as inflammation and immune evasion [54-56].

Additionally, somatic mutations in metabolic and immune-related genes, such as *ASS1* and *SERPINC1*, provide insights into the metabolic reprogramming and immune evasion mechanisms in Lynch syndrome-associated endometrial cancer [57, 58]. *SERPINC1* encodes antithrombin III and might contribute to the hypercoagulable state [28, 59] often observed in cancer patients, potentially linking coagulation pathways to tumor growth and metastasis. A recent study found that targeting *SERPINC1* could represent a new therapeutic approach for patients with liver metastases originating from colorectal cancer [60]. These findings suggest that targeting metabolic pathways and the tumor microenvironment could offer new therapeutic strategies for this patient population. The frequent occurrence of somatic mutations in *PIK3CA* and *PTEN*, consistent with their roles in the PI3K/AKT/mTOR pathway, emphasizes their universal relevance in endometrial cancer and their potential as therapeutic targets, especially since PI3K/Akt/mTOR inhibitors were proven to be effective in treating colorectal cancer associated with Lynch syndrome [61, 62]. The presence of actionable somatic mutations, particularly in the PI3K/AKT/mTOR pathway, opens the possibility for targeted therapies, such as PI3K inhibitors, which are currently being tested in clinical trials [63]. The correlation between specific somatic mutations and clinical outcomes underscores the prognostic significance of these genetic alterations. Patients with *PIK3CA* and *PTEN* mutations may benefit from more aggressive treatment or closer monitoring [64]. These findings reinforce the need for clinical trials focused on the efficacy of targeted therapies in Lynch syndrome-associated cancers, considering the unique genetic context of these patients. In comparing the germline and somatic mutations observed in Lynch syndrome-associated colorectal and endometrial cancers, it is noted that genetic variants such as those in *PIK3CA* and *PTEN* are important in the oncogenic processes of both cancer types and the presence of these mutations across both cancer types suggests a common oncogenic mechanism in Lynch syndrome, where disruptions in critical signaling pathways promote malignancy regardless of tissue origin [65, 66]. Therapeutic strategies targeting these pathways could be effective for treating both colorectal and endometrial cancers in Lynch syndrome patients.

Furthermore, our identification of somatic mutations in metabolic and immune-related genes such as *ASS1* and *SERPINC1* represents a novel contribution to the field. While metabolic reprogramming and immune evasion are well-documented in various cancers [57], their specific roles in Lynch syndrome-associated endometrial cancer have not been extensively studied. Bateman et al. [67] stated that inhibiting ASS1 could offer a novel therapeutic strategy for colorectal cancer by disrupting essential metabolic and metabolite signaling pathways. The presence of these mutations suggests that targeting metabolic pathways and the tumor microenvironment could offer new therapeutic strategies.

Our study also has some limitations. While this study offers valuable insights into the genetic landscape of Lynch syndrome-associated endometrial cancer, several limitations must be acknowledged. The small cohort size of 13 patients limits the statistical power and generalizability of the findings, potentially introducing biases and overrepresenting certain mutations. Additionally, potential biases in sample selection and the use of FFPE tumor samples may affect the accuracy of variant identification. Future research should address these limitations by including larger, more diverse cohorts, utilizing fresh-frozen samples, and exploring the relevance of identified mutations across different Lynch syndrome-associated cancers and populations.

CONCLUSIONS

This study provides important insights into the genomic landscape of Lynch syndrome-associated endometrial cancer, revealing significant parallels with colorectal cancer within the syndrome. By employing whole exome sequencing on both germline and somatic samples, we identified key pathogenic mutations in mismatch repair genes such as *MLH1*, *MSH2* and *MSH6* which underscore the shared mechanisms driving microsatellite instability and tumorigenesis in both cancer types. Additionally, the discovery of actionable somatic mutations in the *PIK3CA* and *PTEN* genes highlights potential therapeutic targets that could be applicable across Lynch syndrome-associated cancers.

The novel identification of mutations in genes involved in the extracellular matrix and tumor microenvironment, such as *FBN1* and *SPARC*, suggests a unique role for these factors in endometrial cancer progression. These findings not only enhance our understanding of the genetic drivers of Lynch syndrome-associated cancers but also point to the importance

of personalized treatment strategies that could improve outcomes for patients affected by this hereditary condition.

Conflicts of interest: None to declare.

Authors' contribution: R.B. and N.S. conceived and designed the study. R.B. and M.P.D. contributed to the methodology, S.R.I. and S.C.V. drafted the manuscript. T.A.G. performed the histopathological diagnosis and contributed to editing the manuscript. S.R.I. and M.P.D. collected the data. V.N.V., S.C.V and C.L.B. interpreted the results.

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